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Measles Structure Offers Drug Design Guide

Despite extensive vaccination efforts, measles remains a dangerous, highly contagious disease worldwide, infecting some 20 million people a year. Structural information about the protein the virus uses to attach itself to its target cells could provide a new strategy to fight infection. A new structure from Howard Hughes Medical Institute (HHMI) researchers reveals important features of the propeller-like molecule, known as measles virus hemagglutinin (MVH), that drug designers will need to consider as they attempt to thwart infection by interfering with the virus's grip on its host cell.

Researchers Jeremy Colf and Sean Joo determined the structure in the laboratory of Howard Hughes Medical Institute investigator Christopher Garcia. The researchers published their findings November 18, 2007, as an advance online publication of the journal *Nature Structural and Molecular Biology*. They are at the Stanford University School of Medicine.

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— K. Christopher Garcia

Colf and Joo employed X-ray crystallography to solve the structure of MVH. In this widely used technique, X-rays are directed through crystals of a protein, allowing the protein's structure to be deduced from the diffraction pattern of the X-ray beam.

The resulting structure revealed that MVH is shaped like a propeller, with its blades spread such that they can attach to the host cell in the infection process. This propeller shape is commonly found on the surfaces of viruses as a protein called a neuraminidase. Viruses such as influenza use a cleft at the center of the propeller to bind carbohydrates on the cells they infect. Neuraminidases act as a kind of general molecular Velcro, sticking the virus to the surface of cells, said Garcia.

One feature that makes the measles virus unique is that it doesn't use carbohydrates to bind to host cells. While MVH exhibits the neuraminidase fold, it is a 'dead' neuraminidase, having lost all function, he said. Rather, the

measles virus hemagglutinin has evolved the ability to bind to two non-overlapping host cell receptors, called SLAM and CD46. This is a completely novel mechanism for this class of viruses. So, if a drug is to block measles virus binding, it has to interfere with both of these receptors.

Garcia said that the structure of MVH provides a starting point to identifying cavities and clefts on the protein surface that one could target with small molecules. The next step, he said, is to solve the structure of MVH complexed with the host cell receptors, to elucidate the details of the host-virus attachment. So far, his group has begun to analyze the structure of MVH complexed with the SLAM receptor.

Once we have high-resolution pictures of the determinants of this attachment interface, it will be possible to begin to think about therapeutic intervention in that attachment, he said.